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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/214,836	10/04/99	FIGDOR	C VEOC.002.00U

HM22/0913
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ART UNIT	**PAPER NUMBER**
1642	12

DATE MAILED: 09/13/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/214,836	Applicant(s) FIGDOR ET AL.	
	Examiner Stephen L. Rawlings, Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,6,7,11,14,15 and 19-29* is/are pending in the application.

4a) Of the above claim(s) *20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6,7,11,14,15,19 and 21-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,2,4,6,7,11,14,15 and 19-29* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The election with traverse filed on January 22, 2001 in Paper No. 10 is acknowledged and has been entered. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. The amendment filed on January 22, 2001 in Paper No. 10 is acknowledged and has been entered. Claims 3, 5, 8-10, 12, 13, and 16-18 are canceled. Claims 1, 4, 6, and 11 are amended. Claims 20-29 are added.

3. Claims 1, 2, 4, 6, 7, 14, 15, and 19-29 are pending in the application. Claim 20 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

4. Claims 1, 2, 4, 6, 7, 14, 15, 19, and 21-29 are currently under prosecution.

Priority

5. Receipt is acknowledged of a certified copy of the EP 96201945.1 application referred to in the oath or declaration. If this copy is being filed to obtain the benefits of the foreign filing date under 35 U.S.C. 119(a)-(d), applicant should also file a claim for such priority as required by 35 U.S.C. 119(b). Furthermore, it is noted that according to the declaration, priority is not being claimed in this application.

6. This application claims benefit of PCT/EP97/03712, which designates the United States. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

Claim Objections

7. Claims 6 and 7 are objected to because of the following informalities: Claim 6 is drawn to the subject matter of a non-elected invention, namely a vaccine comprising a nucleic acid molecule. Claim 7 depends from claim 6. Appropriate correction is required.

8. Claim 19 is objected to because there does not appear to be antecedent basis in the specification for the claim language recited in the claim. Specifically, there appears to be no antecedent basis for "a kit". Appropriate action is required; amending the specification to include proper antecedent basis for "a kit" can obviate this objection. See *In re Benno*, 768 F.2d 1340, 226 USPQ 683 (Federal Circuit 1985).

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 6, 7, and 21-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 6, 7, and 21-26 are drawn to a vaccine comprising the peptide of claim 1, which according to the specification can be used to treat a patient diagnosed with melanoma.

The specification teaches that that gp100 is a melanoma-associated differentiation marker. The specification teaches that tumor-infiltrating cytotoxic T lymphocytes (CTL), which were isolated from a biopsy of a melanoma, recognize a naturally occurring class I Major Histocompatibility Complex (MHC), HLA-A*0201-restricted peptide epitope, which is derived *in vivo* from the melanoma-associated

differentiation marker, gp100. The peptide epitope consists of the sequence of nine amino acids corresponding to amino acids 154-162 of the amino acid sequence of gp100: KTWGQYWQV (SEQ ID NO: 9). The specification teaches that substitution of the amino acid residues at positions 3, 5, 6, 7, or 9 by alanine cause a decrease in the peptide's binding affinity for either HLA-A*0201 or the T cell receptor (TCR) relative to a peptide having the naturally occurring amino acid sequence (i.e., SEQ ID NO: 9). However, the specification teaches that some synthetic analogues of the natural peptide, which differ therefrom by substitution of the amino acid residue at position 2 or 8 of SEQ ID NO: 9 with another amino acid, have increased binding affinity for HLA-A*0201 relative to the natural peptide. Therefore, the claims are particularly drawn to a vaccine comprising a peptide comprising at least part of the amino acid sequence of SEQ ID NO: 9, wherein threonine (T) at position 2 is replaced by either isoleucine (I), leucine (L), or valine (V). Alternatively, the claims are drawn to a vaccine comprising a peptide comprising at least part of the amino acid sequence of SEQ ID NO: 9, wherein glutamine (Q) at position 8 is replaced by alanine (A). The amino acid sequence of the latter peptide is KTWGQYWAV, which is set forth as SEQ ID NO: 1. More specifically, the specification teaches that the HLA-A*0201 binding affinities of these four analogues are comparable to or greater than the HLA-A*0201 binding affinity of the peptide of SEQ ID NO: 9 (page 28, Table I and page 30, Table III). The specification also teaches that one of the analogues (i.e., SEQ ID NO: 1) has an enhanced ability to sensitize HLA-A*0201-expressing target cells to the cytotoxicity of a tumor-infiltrating lymphocyte (TIL) cell line (page 28, Table I). Clearly, according to the disclosure, sensitization of the target cells with the peptide of SEQ ID NO: 1, which has the substitution at position 8, has a greater effect than sensitization with the peptide of SEQ ID NO: 9. However, it is unclear if the difference in the observed cytotoxicities (i.e., percentage of target cells lysed) is statistically significant. Similarly, the specification discloses that the peptide analogues containing a substitution of the threonine residue (i.e., the N-terminal anchor at position 2) are able to cause "improved target sensitization" (page 25, Example 3). However, there again appears to be insignificant differences between the percentages of target cells lysed in the assays using the various peptide analogues relative to the

peptide of SEQ ID NO: 9 (page 29, Table II). The specification teaches that three of these analogues are more immunogenic in transgenic mice that express human HLA-A*0201 than the peptide of SEQ ID NO: 9 (Figure 3 and page 26, paragraph 1). The specification discloses the analogue in which the threonine residue at position 2 is replaced by an isoleucine residue is no more immunogenic than the peptide in which no replacement is made (i.e., SEQ ID NO: 9) (page 26, paragraph 1). However, the analogue in which the threonine residue at position 2 is replaced by a valine residue is also no more immunogenic than the peptide of SEQ ID NO: 9 (Figure 4). The analogue in which the threonine residue at position 2 is replaced by a leucine residue appears to be more immunogenic than the peptide of SEQ ID NO: 9. Nevertheless, a comparison of the data in Figure 4 suggests that the peptide of SEQ ID NO: 9 elicited less cytotoxicity than would normally occur and so it is unclear whether the difference in the levels of cytotoxicity elicited by the peptide of SEQ ID NO: 9 and the leucine-substituted analogue is significant. Evidently, only the peptide of SEQ ID NO: 1 may be significantly more immunogenic in mice (Figure 4). Finally, the specification teaches that bulk cultures of peripheral blood mononuclear cells (PBMC) specifically lyse gp100-expressing target cells after *in vitro* stimulation of in the presence of each of the claimed peptide analogues (page 26 and 27, Example 5). It appears, however, that only the peptide of SEQ ID NO: 1 elicited a greater immune response against gp100-expressing target cells than the peptide of SEQ ID NO: 9 (Figure 5).

A. One cannot extrapolate the teachings of the specification to the enablement of the claims, as drawn to a vaccine for use in *preventing or suppressing* melanoma or metastases thereof in a patient or an animal. Clearly, undue experimentation would be required of one of skill in the art to use the claimed invention with a reasonable expectation of success. In the absence of any teaching to the contrary, such as working exemplification, in the specification, in view of the state of the art, there cannot be a reasonable expectation of success in using the claimed invention. The art of tumor prevention is intractable and certainly, in view of this fact, one's success in practicing the invention is unpredictable.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The prevention of cancer and more particularly melanoma is intractable. The specification does not exemplify the use of the claimed vaccine to prevent cancer in a patient or animal and thus, there is no factual evidence of record that would suggest that a vaccine comprising a claimed immunogenic peptide could be used effectively to prevent or suppress the incidence of primary melanoma and metastases thereof in a patient or animal. In the absence of working exemplification and in view of the high level of unpredictability in the art, one skilled in the art would not accept the assertion that the invention can be used effectively to prevent or suppress the onset of melanoma in a patient or animal.

Certainly not all patients are to be considered for prophylactic therapy, because only some patients will have a potential to benefit from such therapy. Certain antigenic peptide epitopes of a melanoma-associated antigen, such as gp100 may not be displayed in the context of every Major Histocompatibility Complex (MHC) or in other words, bind to every type of HLA molecule. Only patients with a particular HLA type, namely HLA-A*0201 will have a potential to benefit from the use of the invention, since according to specification, the claimed immunogenic peptides are HLA-A*0201-restricted. Furthermore, use of the invention can only be expected to benefit patients by activating CD8+ cytotoxic T lymphocytes (CTL). Contrary to the suggestion on page 11, paragraph 4, there is no factual evidence that the claimed peptides are capable of binding class II MHC molecules to potentially stimulate anti-gp100 antibody production. Accordingly, there is no factual evidence of record indicating that the claimed vaccines are capable of eliciting a humoral immune response.

Nevertheless, the expression of a particular HLA type is not the only criterion that determines whether an individual can be treated using the invention. The process of eliciting an immune response is highly complex. Simplistically, CTL bind to antigen-presenting cells (APC) and under specific circumstances will become activated. The CTL and the APC interface by the highly specific formation of a trimolecular complex comprising the antigenic peptide "primed"-class I MHC molecule, displayed at the surface of the APC, and the T cell receptor (TCR), displayed at the surface of the CTL. Every individual has a relatively unique "repertoire" of T cells or clones, where each clone has a different TCR, which has a different antigenic binding specificity. Thus, some individuals' repertoires may be deficient in one or more CTL that, if present would be activated by the claimed immunogen. Just as patients lacking expression of HLA-A*0201 will fail to benefit from immunization with the claimed vaccines, those patients lacking the appropriate CTL clone will also not benefit from the therapeutic use of the invention. Thus, within the population of HLA-A*0201-expressing patients, some will not respond because they have their repertoire of lymphocytes is incomplete and they lack the necessary T cell. Because the specification does not disclose which TCR types will bind the claimed immunogens, the specification fails to provide a means to identify the population of individuals with whom the invention can be used and thus, fails to provide an enabling disclosure. Again, one skilled in the art cannot use the invention with a reasonable expectation of success without first selecting an appropriate individual for treatment and undue experimentation would be required to determine which population of individuals are appropriate.

In summary of the above, the specification does not exemplify the asserted use of the invention. There are no working examples in which the invention is used to prevent or suppress melanoma or the metastases thereof in a subject. In particular, there are no working examples in which the invention is used to elicit a melanoma-specific HLA-A*0201-restricted CTL-mediated immune response in a patient. Nevertheless, the specification fails to provide a means by which appropriate individuals can be selected for treatment using the invention. Yet, there is no factual evidence of record that the claimed genus of vaccines will have universal utility. In fact, apart from

the requirement of expressing HLA-A*0201, the specification does not disclose which features can be used to distinguish appropriate candidates. Of course, the skilled artisan cannot predict which patients will respond and which will not. Therefore, in view of the state of the art and then in the absence of working exemplification *that is commensurate in scope with the claims*, the skilled artisan would not accept the assertion that the claimed method can be used effectively to prevent or suppress the onset of metastatic melanoma in all patients. Therefore, undue experimentation would be required to use the invention with a reasonable expectation of success, because for each of the claimed species of immunogen, one would necessarily have to first determine which patients will be responsive and then derive a means to identify those patients before proceeding with the treatment.

B. The teachings of the specification cannot be extrapolated to the enablement of the claims, as drawn a vaccine for *treating* melanoma or metastases thereof in a patient or animal, because the art of cancer immunotherapy is highly unpredictable and the disclosure provides insufficient guidance and exemplification that demonstrates that the claimed invention can be used effectively. Therefore, one skilled in the art cannot use the invention with a reasonable expectation of success without need for extensive and undue experimentation. The reason is set forth below:

Again, the factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

Bodey, et al (*Anticancer Research* **20**: 2665-2676, 2000) teach, "while cancer vaccine trials have yielded tantalizing results, active immunotherapy has not yet become an established modality of anticancer therapy" (page 2665, column 2). As to the current state of the art, Bodey, et al comment, "the use of active specific immunotherapy (ASI) for cancer (cancer 'vaccines') is still in its scientific infancy despite several decades of clinical and basic research" (page 2668, column 2). Thus, little has changed to alter the artisans' expectations of the still prospective immunotherapy since the invention was made. Cox, et al (*Science* **264**: 716-719, 1994) teach, "neither adoptive transfer of melanoma-specific CTLs nor specific active immunotherapy with

whole melanoma cells or cell-derived preparations has led to the eradication of melanoma in more than a minority of patients" (page 716, column 2). Then again, even that small note of promise has since faded. Bodey, et al disclose, "ASI in at least one instance may have cured melanoma in a patient with metastatic disease, but that patient developed another immunologically and genetically distinct melanoma" (page 2668, column 2). In the abstract Bodey, et al speculate upon the reasons that ASI is ineffective or lacks efficacy:

> The theoretical basis for all of these approaches is very well founded. Animal models, albeit highly artificial, have yielded promising results. Clinical trials in humans, however, have been somewhat disappointing. Although general immune activation directed against the target antigens contained with a cancer vaccine has been documented in most cases, reduction in tumor load has not been frequently observed, and tumor progression and metastasis usually ensue, possibly following a slightly extended period of remission. The failure of cancer vaccines to fulfill their promise is due to the very relationship between host and tumor: through a natural selection process the host leads to the selective enrichment of clones of highly aggressive neoplastically transformed cells, which apparently are so dedifferentiated that they no longer express cancer cell specific molecules. Specific activation of the immune system in such cases only leads to lysis of the remaining cells expressing the particular TAAs [tumor associated antigens] in the context of the particular human leukocyte antigen (HLA) subclass and the necessary costimulatory molecules. The most dangerous clones of tumor cells however lack these features and thus the cancer vaccine is of little use.

The goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (*Journal of NIH Research* **7**: 46-49, 1995) states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph). Ezzell, et al further teaches that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micro-metastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (page 48, paragraph 6). More recently, Bodey, et al (cited supra) state, "there should be caution about assuming that a single epitope or even a few epitopes combined will be as effective 'crude' materials, which might better be thought of as 'polyvalent'" (page 2668, column 2). Spitler (*Cancer Biotherapy* **10**: 1-3, 1995) recognizes the lack of predictability of the nature of the art when she states, "ask

practicing oncologists what they think about cancer vaccines and you're likely to get the following response: 'cancer vaccines don't work'. Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response" (page 1, paragraph 1).

Whatever avenue the artisan takes, in view of the unpredictability in the art, the rarity and lack of uniformity in the successful application, and the numerous and substantial limitations encountered, the threshold of enablement is high. The specification must enable one of skill in the art to make and to use the invention with a reasonable expectation of success. To have success, the use of the invention must elicit a melanoma-specific CTL response against the immunogenic peptide that results in a substantial, clinically significant benefit to the patient. Boon (*Advances in Cancer Research*, 1992, **58**: 177-210) teaches that for successful application of active immunization in human patients, we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have already occurred in the patient and in such cases, active specific immunization will be fruitless, since anergic TCL cannot be activated, will not proliferate, and are deficient in effector function. Several lines of evidence suggest that large tumor burdens can tolerize, or at least depress the capability to respond against the tumor (page 206, paragraph 2). Furthermore, among other mechanisms, Arceci (*Journal of Molecular Medicine* **76**: 80-93, 1998) teaches, "it has been hypothesized that tumor cells may escape immune recognition and subsequent killing by failing to satisfy one or more of the [...] requirements for T cell antigen recognition and activation. For example, if antigen presentation does not occur because of low or absent expression of MHC or lack of a recognizable tumor antigen, then tumor cells would not be recognized" (page 83, column 2). Areci continues, "on the other hand, if antigen recognition occurs by T cells but tumor cells do not express a costimulatory molecule, then T cells might become anergic to the tumor cells" (page 83, column 2). Notably, Areci teaches, "most solid tumors usually do not express costimulatory molecules" (page 84, column 1); therefore, it is unlikely that use of the invention can effectively immunize a patient against gp100-bearing melanomas.

Moreover, there is considerable art indicating that cancer vaccines are ineffective, *even if antigen-specific T-lymphocytes can be activated by immunization protocols*. Lee, et al (*Journal of Immunology* **163**: 6292-6300, 1999) teach, "although comparative ex vivo sensitization of pre- and postvaccination PBMC [peripheral blood mononuclear cells, such as B- and T-lymphocytes] has identified reproducible, vaccine-specific systemic T cell responses to immunization, in the majority of cases no regression is seen" (page 6292, column 1). In studies similar to those that are set forth in the examples in the specification, Lee, et al teach that melanoma antigen epitopes were identified and that these peptide epitopes were capable of inducing highly specific T cell responses against autologous and some HLA-matched tumor cells. Lee, et al disclose that "these studies gave the impression that vaccines induce powerful immunizations comparable to those demonstrable against common pathogens such as the influenza virus to which individuals are repeatedly exposed throughout their lifetime". However, "in most cases, this **vaccine-induced T cell reactivity still does not lead to tumor regression**" (emphasis added) (page 6299, column 1). One of the reasons for the discrepancy, Lee, et al suggest, may be that in vitro methods, which are commonly used to assess immune post-vaccination immune response, such as cell-mediated cytotoxicity assays, tend to "overestimate quantitatively the strength of the immune reaction within the organism" (page 6299, column 1). Lee, et al catalog a variety of possible explanations for the lack of efficacy, including clonal deletion, exhaustion, or senescence, which are implicated in the development of systemic, epitope-specific immune tolerance, and inadequate immune response attributable to decreased T cell receptor signaling capacity or circulating immune-suppressive cytokines, but conclude that their data suggest that the extent rather than the quality of the response might be more significant limitation of the vaccination protocol (page 6299, column 2). More specifically, Lee, et al report that "we were surprised at the relatively low numbers of CTL precursors after vaccination even in patients' samples that boasted an exceptional epitope-specific expansion in vitro" (page 6299, column 2). Lee, et al summarize their study, teaching that "a peptide-based vaccine can effectively generate a quantifiable T cell-specific immune response in the PBMC of cancer patients, though

such a response does not associate with a clinically evident regression of metastatic melanoma" (abstract). While Lee, et al refer specifically to the treatment of melanoma using a different epitope, the teachings are highly germane to the enablement issues relevant in the instant application, because the severe limitations will undoubtedly be shared by both protocols, and there is no exemplification in the specification that would suggest otherwise. In yet another example, Zaks, et al (*Cancer Research* **58**: 4902-4908, 1998) teach that immunization of patients diagnosed with cancer with a peptide epitope derived from the tumor antigen HER-2/neu/ErbB2 leads to activation of peptide-specific cytotoxic T-lymphocytes, but that the T-lymphocytes fail to recognize tumor cells that express the antigen. Zaks, et al disclose that their experience is not unique (page 4907, column 2). Gao, et al (*Journal of Immunotherapy* **23**: 643-653, 2000) found that although antitumor CTL response was enhanced by immunization, the tumors failed to regress. Gao, et al teach that the lack of regression was associated with a lack of CTL migration to the tumor sites (abstract). Thus, activation of peptide epitope-specific CTL is not an appropriate endpoint and a prediction or estimation of efficacy based only upon such data is imprudent or inexact.

Moreover, many attempts to provide efficacious therapeutic or prophylactic immunotherapy for melanoma patients have paradoxically failed; despite evidence of that vaccination has induced proliferation of tumor antigen-specific CTL, no major protective antitumor response was seen in these cases. See, for example, Hu, et al, *Cancer Research* **56**: 2479-2483, 1996; Jaeger, et al, *International Journal of Cancer* **66**: 162-169, 1996; Mukherji, et al, *Proceedings of the National Academy of Science USA* **92**: 8078-8082).

Timmerman, et al (cited supra) teach that Mukherji and colleagues used peptide-pulsed dendritic cells to immunize patients against melanoma (pages 519-520). In this study, while vaccination could elicit peptide-reactive cytotoxic T-lymphocytes (CTL) in patients with advanced melanoma, "despite the presence of these CTL precursors in the vaccination site, peripheral blood, and distant tumors sites, no significant responses were seen". This result echoes the teachings of Lee, et al (cited supra): "thus, a paradoxical coexistence of immune competent T cells and their respective targets

appears to occur in vivo as judged from reagents characterized ex vivo" (page 6298, column 1). In other words, despite the presence of detectable numbers of tumor infiltrating, activated peptide-specific T-lymphocytes, as Timmerman, et al discloses, "no form of active specific immunotherapy has been proven to routinely induce clinically meaningful anti-tumor response" (page 508, paragraph 1). Wen and colleagues also have reported similar unsuccessful findings when using dendritic cells at as an adjuvant in tumor antigen peptide epitope immunization for treatment of multiple myeloma (see Timmerman, et al, page 519, paragraph 1). Again, despite the detection of antigen-reactive T-lymphocytes in the patients following immunization, clinical response was not observed. It is apparent that the use of cancer vaccines has met with little and insignificant clinical success. Accordingly, in view of the unpredictability and general lack of success in the art, given the information presented in the specification alone, one skilled in the art cannot predict whether the claimed method can be used effectively to treat melanoma in mammals, particularly humans. In the absence of exemplification, teaching that the invention can be used efficaciously, one skilled in the art cannot practice the claimed method with a reasonable expectation of success, and accordingly would be forced into undue experimentation in order to practice the invention.

Still other limitations exist, which necessitate the disclosure of working exemplification to overcome the lack of predictability in the art. Certainly, it would not be expected that a melanoma that does not express gp100 would be adversely affected by immunotherapy specific to an immunogen derived from said protein. de Vries, et al (*Cancer Research* **57**: 3223-3229, 1997) teach that not all melanomas express gp100 (abstract). Moreover, tumors are mosaics, composed of some cells that express a particular tumor-associated antigen and others that do not. Consistently, de Vries, et al also teach that analysis of clinical specimens shows that gp100 is heterogeneously expressed in as many as 50% of lesions (page 3228, column 1). Thus, paradoxically, vaccination against melanoma cells expressing gp100 may only serve to select those cells that do not express the antigen for continued survival. In fact, there is evidence that melanomas evolve to repress expression of gp100, perhaps to evade the host's antitumor immune response. De Vries, et al teach that 17% of the advanced primary

and metastatic melanomas do not express the differentiation antigens, including gp100, which are commonly targeted by antitumor vaccines (abstract). Slingluff, et al (Cancer Immunology & Immunotherapy 48: 661-672, 2000) also teach that examples of melanomas with concordant loss of expression of multiple differentiation antigens and are thus resistant to active specific immunotherapy directed against cells that express gp100 and other antigens (abstract). At the very least the teachings of de Vries, et al and Slingluff, et al teach that one skilled in the art cannot predict whether a HLA-A*0201-expressing patient will benefit from the use of the invention. It is reasonable to infer from their teachings that patients must be carefully selected for treatment (e.g., it should be determined whether the patient's melanoma expresses gp100 and also whether the tumor homogenously expresses gp100). Again, there is insufficient guidance in the specification to enable one skilled in the art to select appropriate candidates for therapy. Therefore, one cannot extrapolate the teachings of the specification to the enablement of the invention commensurate in scope with the claims.

Furthermore, the immunogenic peptides encompassed by the claims may not elicit a *specific* immune response against melanoma. The specificity of the immune response in humans or other animals to the vaccine can only be determined empirically. The substitutions in the amino acid sequence of a naturally occurring peptide epitope may enable inappropriate activation of other non-gp100-specific CTL. The stimulation of a non-specific immune response can be deleterious to the mammal, possibly inducing autoimmune disease in the mammal. As such, one would be forced into undue experimentation to determine which of the broadly claimed species of immunogen are capable of producing the desired specific immune response without adversely affecting the patient.

Furthermore, in using synthetic amino acid sequences as immunogens, it is well known in the art that one cannot be certain how well such a peptide will elicit a CTL response *in vivo*. Although the specification clearly demonstrates the immunogenicity of the claimed peptides *in vitro*, there is no way to determine whether the CTL produced will actually affect melanoma cells *in vivo*. A demonstration that a peptide is immunogenic in mice is not sufficient evidence that the peptide will elicit a specific

immune response in humans. The specification does not take into account the conformation or three-dimensional folding of the native peptide epitope, its glycosylation and other post-translational modifications, or other characteristics that are of significant importance in peptide recognition by the class I MHC molecule and TCR. Peptides or synthetic antigens, therefore, cannot always reliably substitute for the natural tertiary and quaternary structure of a peptide in a physiological situation. Zaks, et al (cited supra) teach, "it is possible that reactive CTL [cytotoxic T-lymphocytes] recognize a peptide conformation that is present in solution but different from the one conferred by endogenous presentation" (page 4907, column 2). However, again, there is no evidence of record that indicates that CTL activated by immunization using the claimed vaccine will be capable of recognizing a tumor *in vivo* and more particularly a tumor in a human subject.

Finally, with regard to the lack of success in their studies of peptide immunization against cancer, Zaks, et al, teach another limitation of the approach: "the theoretical probability of any given epitope being expressed, in sufficient quantities, by an MHC allele are small" (page 4906, column 2). Therefore, while tumor cells may express gp100, the level at which the antigen (i.e., peptide epitope) is presented at the cell's surface, in the context of the MHC class I molecule, may be inadequate to provide clinical efficacy, even though peptide epitope-specific T-lymphocytes are activated, which are capable of mediating selective cytotoxicity against tumor cells that display the epitope. For this reason, it is unlikely that a vaccine composed of a single peptide epitope will prove effective in antitumor immunotherapy. As previously stated, there is no factual evidence that indicates that the peptide-specific T-lymphocytes can actually be produced in response to the components of the claimed vaccines in humans. Certainly, one skilled in the art cannot predict the extent of the immune response (i.e., the number of activated peptide-specific T lymphocytes), which might be induced by the invention. Certainly, as the teachings of Zaks, et al suggest, an insufficient immune response, comprising only a small number of activated peptide-specific T lymphocytes, will substantially limit the efficacy of the claimed method for preventing or treating cancer in a mammal. There are many reasons that the promise of pre-clinical

endeavors is broken once clinical trials ensue. Among the possible reasons, with regard to animal models of disease, Timmerman, et al (cited supra) teach, "although [...] results demonstrate in vivo activity of antigen-pulsed DC [dendritic cell] vaccines against tumors, the model systems employed are highly artificial; in these experiments, genes encoding foreign proteins are introduced into tumors to serve as model tumor antigens. Such tumors tend to be highly immunogenic and thus quite unlike most human cancers" (page 514, paragraph 2). With regard to the comparative assessment of pre-and post-vaccination peripheral blood mononuclear cells (PBMC) for tumor-specific expansion, Lee, et al (cited supra) teach, "it is likely that the immune responses judged after ex vivo expansion of postvaccination PBMC overestimate quantitatively the strength of the immune reaction within the organism" (page 6299, column 1). Nevertheless, the magnitude of response that might be sufficient to protect a mammal against a tumor is unknown. Yamshchikov, et al (*Clinical Cancer Research* **7**: 909s-916s, 2001) teach, "little is known about the frequency of CTLs reactive to tumor-associated antigens in patients, nor is there a clear understanding of the level of CTL reactivity in vivo that is required for immunological control of tumor progression" (page 909s, column 2).

C. Success in the art of cancer therapy is highly unpredictable. Gura (*Science* **278**: 1041-1042, 1997) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile (abstract). Gura teaches that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models, but that only 39 have actually been shown to be useful for chemotherapy (page 1041, first and second paragraphs). Clearly, one skilled in the art cannot predict whether an invention can be used successfully. Ironically, with regard to antitumor vaccines, Sinkovics, et al (*International Journal of Oncology* **16**: 81-96, 2000) teach, "certain human tumor (melanoma) cell vaccines instead of producing antitumor immunity actually enhanced tumor growth" (page 82, column 1). Clearly, therefore, in the absence of working exemplification, one skilled in the art could not use the invention

with a reasonable expectation of success and would be forced to perform extensive, undue experimentation to determine even if the invention might be used successfully.

D. Finally, Bodey, et al teach that despite promising, even tantalizing results *in vitro* and *in vivo*, especially with animal models, the failure of cancer vaccines is predicated by very relationship between the tumor and the host immune system, which effectively makes the use of cancer vaccines futile:

> Malignant tumors undergo constant microevolution. Natural selection of the most advantageous surface IP [immunophenotype] involves constant modulation of previous IPs. Progressive dedifferentiation characterizes all neoplastically transformed cells. During this process, numerous 'novel' cell surface antigens appear, are modified and thus do not present the host's immune system with some immunogenic elements. The leukocytic inflammatory infiltrate contains cells with divers capabilities including neutrophils, macrophages and other professional APCs [antigen-presenting cells], as well as T lymphocytes. In situ activation of TAA [tumor-associated antigen] specific CTL [cytotoxic T-lymphocyte] clones occurs and thousands of tumor cells are lysed. However, as we would expect from any population in danger of extinction, the cells of the neoplastically transformed mass proceed with their microevolution and numerous clones of tumor cells survive each repeated attack by the immune system through secretion of immunoinhibitory cytokines, downregulation of MHC molecules, loss of costimulatory molecules, and induction of clonal T cell anergy, among other as yet uncovered ways. This process continues until the 'creation' (ironically as it may sound, by the host's immune system) of highly resistant, poorly immunogenic, and extremely aggressive clones of tumor cells. This is the reality of cancer progression: a back-and-forth struggle between host and tumor, with evolutionary dynamic exchanges throughout the entire process. Use of cancer vaccines to stimulate the immune system may be in vain" (citations omitted) (pages 2673-2674).

In summary, the specification provides no factual evidence that the claimed means and method can be used effectively to prevent or treat cancer in a patient or animal. Even though a peptide-specific immune response may be observed in patients receiving the vaccine composition, there is no factual evidence that the patient's condition would clinically improve. Based upon the teachings of Lee, et al (cited supra), Zaks, et al (cited supra), and the others referenced herein, it is evident that eliciting an immune response is not sufficient to evoke a clinically significant or specific antitumor effect. Therefore, because of the demonstrated unpredictability in the art of cancer immunotherapy, in the absence of sufficient exemplification and guidance, one skilled in the art cannot practice the claimed method with a reasonable expectation of success.

Consequently, one would be forced into undue experimentation to practice the invention commensurate in scope with the claims with a reasonable expectation of success.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1, 2, 4, 6, 7, 11, 14, 15, 19, and 21-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 4, 6, 7, 14, 15, 19, and 21-26 are vague and indefinite because claim 1 recites the phrase "immunogenic with lymphocytes". The use of the phrase renders the claim indefinite because it is unclear if the claim requires the peptide to be immunogenic *together with* lymphocytes directed against metastatic melanomas or to be immunogenic of an immune response comprising activation of lymphocytes. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claims 1, 2, 4, 6, 7, 14, 15, 19, and 21-26 are vague and indefinite because claim 1 recites the phrase "directed against metastatic melanomas". The use of the phrase renders the claim indefinite because it is unclear if the claim requires the peptide to be immunogenic of an immune response comprising lymphocytes that actually cause the specific destruction of metastatic melanomas or merely to be immunogenic of an immune response comprising lymphocytes that are targeted to metastatic melanomas. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claim 6, 7, and 21-26 are vague and indefinite because claim 6 recites the phrase "an epitope thereof". The use of the phrase renders the claims indefinite because the specification teaches that the peptide is an epitope and it is unclear that there can be epitope within an epitope, because an epitope is ordinarily defined as the minimal binding determinant specifically recognized by the complementarity determining regions of an immunoglobulin-like molecule. Nevertheless, according to claim 1 the

peptide *comprises* at least part of the amino acid sequence of SEQ ID NO: 9 wherein an original amino acid at position 2 or 8 is substituted with a replacement amino acid and wherein said peptide is immunogenic with lymphocytes directed against metastatic melanomas. There is no disclosure of the nature of the other material of which the peptide may comprise. Consequently, it is unclear whether the claim is intended to encompass a vaccine comprising a peptide of claim 1 comprising an epitope thereof that is recognized by an antibody that binds a protein other than gp100. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claim 21 and 24 are indefinite because claim 21 recites the phrase "the peptide has an alanine at position 8 or is an epitope of said peptide". In the alternative, the reads, "the peptide is an epitope of said peptide". The claim infers that an epitope is part of a peptide. It is unclear how the peptide can be part of the peptide, when the peptide is the peptide. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention.

Claim 28 is vague and indefinite because the claim recites the term "further" in line 1. The use of the term "further" renders the claim vague and indefinite. Claim 11, to which claim 28 is drawn, recites the limitation "wherein an original amino acid at position 2 or 8 of SEQ ID NO: 9 is substituted with a replacement amino acid". It is unclear to which other limitation the term "further" refers and therefore one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention. Nevertheless, if the claim is intended to encompass a peptide wherein the original amino acid at both positions 2 and 8 is replaced, the claim is drawn to a non-elected invention.

13. Claims 11 and 27-29 are rejected under 35 U.S.C. 112, second paragraph, because claim 11 is incomplete for omitting an essential step, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is: (a) a step in which the antigen-lymphocyte complex is distinguished and separated from lymphocytes that are not associated with antigen.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

15. Claims 1, 2, 6, 7, 11, 14, 22, 25, and 28 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent No. 5,844,075 A.

Claim 1 is drawn to a peptide comprising at least part of the amino acid sequence of SEQ ID NO: 9 wherein an original amino acid at position 2 or 8 is substituted with a replacement amino acid and wherein said peptide is immunogenic with lymphocytes directed against metastatic melanomas. Claim 2 is drawn to the peptide of claim 1, wherein said original amino acid at position 2, threonine, is substituted by a replacement amino acid selected from the group consisting of isoleucine, leucine, and valine. Claims 6, 7, 22, and 25 are drawn to a vaccine comprising the peptide of claim 1 and a pharmaceutically acceptable carrier. Claims 11 and 28 are drawn to a method for isolating melanoma antigen reactive tumor infiltrating lymphocytes, wherein said method comprises reacting said lymphocytes with the peptide of claim 1 or 2, respectively. Claim 14 is drawn to a conjugate of a peptide according to claim 1 and a detectable marker. Claim 19 is drawn to a kit comprising the conjugate of claim 14 or 15.

US Patent No. 5,844,075 A teaches a vaccine comprising a pharmaceutically acceptable carrier and a peptide comprising at least part of the amino acid sequence of SEQ ID NO: 9 wherein an original amino acid at position 2 or 8 is substituted with a replacement amino acid and wherein said peptide is immunogenic with lymphocytes directed against metastatic melanomas, wherein said original amino acid at position 2, threonine, is substituted by a replacement amino acid selected from the group consisting of isoleucine, leucine, and valine. US Patent No. 5,844,075 A also teaches a

method for isolating melanoma antigen reactive tumor infiltrating lymphocytes, wherein said method comprises reacting said lymphocytes with the peptide of claim 1 or 2, respectively. US Patent No. 5,844,075 A also teaches that the peptides of can be conjugated to molecules that can be detected. US Patent No. 5,844,075 A also teaches that the conjugated peptides can be packaged in a kit. See abstract; column 3, lines 41-51; column 12, lines 8-53; column 16, lines 9-30; column 17, lines 22-35; columns 28-29, 41-43, and 60; columns 56 and 57, Table 15; and columns 58 and 59, Table 18.

All the limitations of the claims are met.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claim 1, 2, 6, 7, 11, 14, 15, 22, 25, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,844,075 A.

Refer to the 35 USC § 102(e) rejection above for an analysis of claims 1, 2, 6, 7, 11, 14, 22, 25, and 28. Claim 15 is drawn to a conjugate of a peptide according to claim 1 and a detectable marker, wherein said detectable marker is a radionuclide.

US Patent No. 5,844,075 A teaches a peptide according to claim 1. US Patent No. 5,844,075 A also teaches that which is set forth in the 35 USC § 102(e) rejection above, but does not explicitly teach a conjugate of a peptide and a radionuclide.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to conjugate the peptide of US Patent No. 5,844,075 A to and a radionuclide, because the presence of the conjugated peptide would be detectable.

One of ordinary skill in the art at the time the invention was made would have been motivated to make and use a conjugate the peptide of US Patent No. 5,844,075 A

and a radionuclide, because the conjugate could facilitate detection of CTL that bind the peptide and it would be useful to separate CTL that bind the peptide from CTL that do not bind the peptide since such a separation would reduce non-specific background cytotoxicity resulting from spurious non-peptide-specific effector activity.

Double Patenting

18. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

19. Applicant is advised that should claim 21 be found allowable, claim 23 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

20. Applicant is advised that should claim 24 be found allowable, claim 26 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing

one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

21. Applicant is advised that should claim 27 be found allowable, claim 29 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Conclusion

22. No claims are allowed.

23. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr

September 8, 2001

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